OCCURRENCE OF HYPOTHYROIDISM IN CHRONIC LIVER DISEASE AND CORELATION OF FREE TRIIDOTHYRONINE WITH CHILD PUGH SCORE

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CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled "**OCCURRENCE OF HYPOTHYROIDISM IN CHRONIC LIVER DISEASE AND CORELATION OF FREE TRIIDOTHYRONINE WITH CHILD PUGH SCORE**" is the bonafide work of **Dr. M.CHANDRA SHEKAR** in partial fulfillment of the University regulations of The Tamilnadu Dr.M.G.R Medical University, Chennai, for the award of degree of Doctor Of Medicine (M.D) Branch-I -General Medicine.

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DECLARATION

I, **Dr. M.CHANDRA SHEKAR**, hereby declare that,I carried out this work entitled "**OCCURRENCE OF HYPOTHYROIDISM IN CHRONIC LIVER DISEASE AND CORELATION OF FREE TRIIDOTHYRONINE WITH CHILD PUGH SCORE**" at Kanyakumari Government Medical College Hospital, Asaripallam, under the guidance of **Prof. Dr. Christopher Nesamony. M.D.,** Professor of Medicine ,during the period of one year .I also declare that this bonafide work has not been submitted in part or full by me or any others for any award, degree or diploma to any other University or Board either in India or abroad.

This is submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of the University rules and regulations for the award of degree of Doctor Of Medicine (M.D) Branch- I-General Medicine.

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INTRODUCTION

Liver disease are most common all over the world (prevalence being 4-17.5percent) as well as in India and the prevalence of liver disease likely to be increased in future [(1)]. Among the various functions of liver, one function is synthesis of carrier proteins and metabolism of hormones. Thus liver diseases, have been shown to be associated with various endocrinal disturbances[(2,3)]. The liver dysfunction leads to secondary dysfunction of endocrine glands directly due to the toxic effects and indirectly by the alteration of the carrier protein synthesis. Therefore ,chronic liver disease may be accompanied by signs of apparent hormonal imbalance.

Thyroxine and Tri-iodothyronine are essential for normal organ growth, development and function. These hormones regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. Liver

plays an important role in the metabolism of thyroid hormone like conjugation, peripheral deiodination and synthesis of thyroid binding globulin[4-7.)]Hence ,it is not surprising that thyroid dysfunction have been reported in various spectra of liver disease and associated with severity of liver disease[8-10].

"NORMAL THYROID FUNCTION IS DEPENDENT ON A NORMALLY FUNCTIONING THYROID AND LIVER AXIS"

In normal subjects, thyroid gland secretes 110nmol of thyroxine and 10nmol of tri- iodothyronine each day. Even though Thyroxine is secreted at a higher rate quantitatively , it is regarded as a pro hormone that requires de-iodination and conversion to T3 to become biologically active.

Iodo-thyroxineselenodeiodinase

Enzyme system (D1, D2)

T4----------→T3

This reaction occurs in thyroid and extrathyroidal system. Extrathyroidal includes Liver, kidney and Pitutary. Out of this about 30-40 percent of extrathyroidal conversion occurs in Liver.

Inspite of this, LIVER also plays an important role in inactivation of thyroid hormones by D3. In addition to central role in de iodination to active and deactive thyroid hormones, the liver performs specific functions relating to thyroid hormone transport. >99% of thyroid hormones bound to thyroxine binding globulin, thyroid binding prealbumin and albumin in plasma. The free hormone component is in equilibrium with protein bound component and this free form is available for metabolic function.

Various studies indicated that during various phase of liver disease the serum T4 concentrationaltered accordingly and related also to the disease progression. T3 can be used as

good laboratory index in evaluating the status of liver disease. The serum T3 concentration and those liver factors, such as bilirubin are now can be regarded as valuable index in the following the trends in thyroid-liver patho physiology. It is vital to measure the free and T4 thyroid Stimulating Hormone (TSH) and any other laboratory test which may be in any help to avoid misdiagnosis of a hypothyroid patients suffering from liver diseases. Few endocrinedisorders associated with CLD are even reported to reverse after liver transplantation[6].The low total and FT3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal BMR within hepatocytes and preserve liver function and total body protein stores[5].It has been suggested that this adaptation may confer a survival advantage, which adapts an organism to chronic illness by reducing the basal metabolic rate within cells and thereby reducing caloric requirements.

Hence the present study is to establishing the concrete relationship between hypothyroidism (by measuring FT3, FT4, TSH) and chronic liver disease and consider FT3 as the factor of severity by correlating with child-pugh score by using clinical and biochemical parameters available in our hospital.

REVIEW OF LITERATURE

Chronic liver disease in the clinical context is a disease process of the liver that exceeds more than 6 months, that involves a process of progressive destruction and regeneration of the liver parenchyma that leading to fibrosis and cirrhosis[11]. Patients with a history of chronic liver disease with gastroesophageal varices, ascites, or hepatic encephalopathy are likely to have cirrhosis, and liver biopsy is not essential in such cases for confirming cirrhosis. In patients with a diagnosis of chronic liver disease without these complications, physical findings of an enlarged left hepatic lobe with splenomegaly, along with the cutaneous stigmata of liver disease suggestive of cirrhosis, especially in the setting of thrombocytopenia and impaired hepatic synthetic function (e.g., hypoalbuminemia, prolongation of the prothrombin

time). If physical and laboratory findings are not suggestive of cirrhosis, imaging studies can help make a diagnosis of cirrhosis. A small nodular liver with splenomegaly and intra-abdominal collaterals and the presence of ascites on abdominal US (or other cross-sectional imaging study) suggests cirrhosis[12].This process distorts the normal liver architecture, interferes with blood flow through the liver and disrupts the functions of liver.

Classification of cirrhosis:

1.MORPHOLOGICAL CLASSIFICATION:

Cirrhosis was historically classified morphologically as micronodular, macronodular and mixed.

Micronodular cirrhosis, characterized by nodules less than 3mm in diameter, was believed to be caused by alcohol, hemochromatosis, cholestatic causes of cirrhosis and hepatic venous outflow obstruction.

Macronodular cirrhosis, characterized by various sized nodules more than 3mm in diameter was believed to be secondary to chronic viral hepatitis.

Although important from a historical perspective, the morphological classification system has number of limitations and has thus largely been abandoned. First, it is relatively non specific with regard to etiology. Second, the morphological appearance of the liver may change as the liver disease progresses; micronodular cirrhosis usually progresses to macronodular cirrhosis.

Third, serological markers available today are more specific than morphological appearance of the liver for determining the etiology of cirrhosis.

2.ETIOLOGICAL CLASSIFICATION OF CIRRHOSIS

Classification of cirrhosis according to etiology as this approach may help to determine prophylactic and therapeutic measures as well as prognosis. If all diagnostic options are employed and the patient cooperates optimally. An etiological identification of cirrhosis is possible in almost all cases today. Due to improved detailed diagnostic options, the group of so called cryptogenic cirrhosis has been consistently reduced(<10% of cases).

HEPATITIS AND OTHER VIRUSES:(post hepatitis)

Worldwide, hepatitis B is the most common cause of cirrhosis, but in Egypt and United states hepatitis C is the most common cause.

Three viruses are responsible for post-hepatic cirrhosis, HBV,HCV and HDV. The latter is a defective organism which can replicate when co-infection with HBV is present.

Chronicinfection with these viruses account for the majority of the cases of chronic active hepatitis which give rise to post-hepatic cirrhosis.

AUTOIMMUNE HEPATITIS:

In autoimmune hepatitis the body's immune system attacks the liver causing cell damage that leads to cirrhosis.

TOXIC AND DRUG INDUCED

Alcoholic liver disease, it encompasses the hepatic manifestations of alcohol over consumption, including fatty liver, alcoholic hepatitis, chronic hepatitis with hepatic fibrosis or cirrhosis. Although steatosis(fatty liver) will develop in any individual who consumes large quantity of alcohol beverages over a long period of time, this process is transient a reversible. Of all chronic heavy drinkers, only 15-20% develop cirrhosis or hepatitis, which can occur concomitantly or in succession. Chronic consumption of

alcohol results in the secretion of pro inflammatory cytokine (TNF-alpha, Interleukin 6 and Interleukin 8) and oxidative stress. These factors cause inflammation, apoptosis and eventually fibrosis of liver cells.

- Drugs like amiodarone, methotrexate, nitrofurantoin may lead to cirrhosis.

METABOLIC

- Non-alcoholic fatty liver disease – NAFLD is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver. A subgroup of NAFLD patients displays liver cell injury and inflammation in addition to excessive fat(steatohepatitis). The latter condition, designated NASH, is virtually indistinguishable histologically from alcoholic steatohepatitis.

- Hemochromatosis.
- Wilson’s disease.

COMPLICATIONS

1. Variceal bleeding- Variceal bleeding is caused by portal hypertension, which is an increase in the pressure within the portal vein (the large vessel that carries blood from the digestive organs to the liver). This increase in pressure is caused by a blockage of blood flow through the liver as a result of cirrhosis. Increased pressure in the portal vein causes other veins in the body to enlarge (varices), such as those in the esophagus and stomach, it bypass the blockage. These varices become fragile and can bleed easily, causing severe hemorrhagic and fluid in the abdomen.

2. Hepatic encephalopathy: hepatic encephalopathy most often occurs when cirrhosis has been present for a long

time. Toxins produced in our intestines are normally detoxified by the liver, but once cirrhosis occurs, the liver cannot detoxify as well. Toxins get in to the bloodstream and can cause confusion, changes in behavior and even coma.

3. Ascites: It is the accumulation of the fluid in the peritoneal cavity due to increase in intrahepatic resistance, increased portal pressure, vasodilation of splancnic arterial system and hypoalbuminemia.

4. Synthetic dysfunction:

   a.Hypoalbuminemia

   b.Coagulopathy

5. Hepatopulmonary syndrome: Liver cirrhosis can lead to hepatopulmonary syndrome characterized by platypnea and orthodeoxia.

6. Hepatorenal syndrome-Functional renal failure within renal pathology occurring in about 10%of patients with advanced cirrhosis due to increased in renal vascular resistance accompanied by a reduction in systemic vascular resistance.

7. Hepatocellular carcinoma.

Child pugh scoring-

It was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation.

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicates most severe derangement.

MEASURE	1 POINT	2 POINTS	3 POINTS
Total bilrubin,µmol/l(mg/dl)	<34(<2)	34-50(2-3)	>50(>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4

Chronic liver disease is classified into Child-pugh class A to C, employing the added score from above

POINTS	CLASS	ONE YEAR SURVIVAL	TWO YEAR SURVIVAL
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Physiology of the hypothalamic-pitutary-thyroid axis: a short review

The thyroid gland participates with the hypothalamus and pituitary in a classic feedback control loop. There is a close relationship among the hypothalamus, the anterior pituitary, the thyroid gland and still higher centers in the brain, the function of the entire complex being modi□ed in a typical negative-feedback manner by the availability of the thyroid hormones. The parvocellular region of the paraventricular nuclei of the hypothalamusis the source of the TRH that regulates TSH secretion. TRH travels in the axons of the peptidergic neurons through the median eminence and is released close to the hypothalamic-pituitary portal plexus.

Thyrotropin (TSH) is the major regulator of the morphologic and functional states of the thyroid. TRH increases and thyroid hormone suppresses, and these are the

two most important infuences on TSH synthesis. In normal serum, TSH is present at concentrations between 0.5 and 5.0 mU/L. The level is increased in primary hypothyroidism and reduced in thyrotoxicosis. The plasma TSH half-life is about 3 minutes, and production rates in humans are 40 to 150 mU/day. Circulating TSH displaysboth pulsatile and circadian variations. The former are characterized by □uctuations at 1- to 2-hour intervals. The magnitude of TSH pulsations is decreased during fasting orillness and after surgery. The circadian variation is characterized by a nocturnal surge that precedes the onset of sleep and appears to be independent of the cortisol rhythm and of fluctuations in serum T4 and T3 concentrations[13].There is a linear inverse relationship between the serum free T4 concentration and the log of the TSH, making the serum TSH concentration an exquisitely sensitive indicator of the thyroid state of patients with an intact hypothalamic-pituitary axis.

Measurement of serum TSH is the primary screening test for thyroid function. TSH levels vary diurnally by up to approximately 50% of mean values[14].TSH secretion is very sensitive to both minor increase and decrease in serum FT4, and abnormal TSH levels occur during developing hypothyroidism and hyperthyroidism before FT4 abnormalities are detectable[15].

Somatostatin (somatotropin release-inhibiting factor [SRIF]), acting through inhibitory G protein (Gi), decreases TSH secretion in vitro and in vivo, but prolonged treatment with a somatostatin analogue does not cause hypothyroidism[16,17]. Similar acute effects occur during dopamine infusion and the administration of bromocriptine, a dopamine agonist; both of these agents inhibit adenylatecyclase. Conversely, blockade of the dopamine receptor by metoclopramide increases the basal serum TSH concentration in both euthyroid and hypothyroid patients.

These findings indicate that dopamine is a regulator of TSH secretion, but chronic administration of dopamine agonists (e.g., for the treatment of prolactinoma) does not cause central hypothyroidism, indicating that compensatory mechanisms negate these acute effects[(18)].

Neurotransmitters are important direct and indirect modulators in TSH synthesis and secretion. A complex network of neurotransmitter neurons terminates on the cell bodies of hypophysiotropic neurons, and several neurotransmitters (e.g., dopamine) are directly released into hypophyseal portal blood, exerting direct effects on anterior pituitary cells. Furthermore, many dopaminergic, serotoninergic, histaminergic, catecholaminergic, opioidergic, and GABAergic systems project from hypothalamic orother brain regions to the hypophysiotropic neurons involved in TSH regulation.

IODINE AND THE SYNTHESIS AND SECRETION OF THYROID HORMONES

The function of the thyroid gland is to generate the quantity of thyroid hormone necessary to meet the demands of the peripheral tissues. This requires iodide uptake by the thyroidal sodium-iodide symporter (NIS), its transfer to the colloid, and its oxidation by thyroid peroxidase (TPO).

TPO also catalyzes the coupling of two molecules of DIT or one ofDIT and one of MIT, leading to formation of T4 and T3, respectively (see late discussion). These products are then stored within the colloid, still as part of the Tg molecule. Pinocytosis of stored colloid leads to the formation of phagolysosomes,the colloid droplets in which Tg is digested by speci□c proteases to release T4, T3, DIT, and MIT as the droplet is translocated toward the basal portion of the cell. T4 and T3 are transported out of the phagolysosomes and across

the basolateral cell membrane, exit the cell, and enter circulation; DIT and MIT are deiodinated by the iodotyrosine dehalogenase to allow recycling of the iodide.

THYROID HORMONES IN PERIPHERAL TISSUES

A wide variety of iodothyronines and their metabolic derivatives exist in plasma. Of these, T4 is highest in concentration and the only one that arises solely from direct secretion by the thyroid gland. In normal humans, T3 is also released from the thyroid, but approximately 80% is derived from the peripheral tissues by enzymatic removal of a single 5' iodine atom from T4 (outer ring or 5' monodeiodination)[19].

The plasma proteins with which T4 is mainly associated are TBG, transthyretin (TTR, formerly termed T4-binding prealbumin [TBPA]), and albumin . About 75% to 80% of T3 is bound by TBG, and the remainder by TTR and albumin. Because TBG is the principal T4- and T3-binding protein,

changes in TBG or its binding are paralleled by changes in total plasma T4 and T3 even though T4 and T3 production is little changed.

The TBG binding site has an affnity for T3 that is about 20-fold less than that for T4.

The affinity of albumin for T4 and T3 binding is much lower than that of either TBG or TTR, but because of its high concentration this protein binds 10% of the plasma thyroid hormones. Between 3% and 6% of plasma T4 and T3 are bound to lipoproteins. In normal serum, the free T4 is approximately 0.02% of the total (about 20pmol/L, or 1.5ng/dL). The approximately 20-fold lower affinity of TBG for T3 results in a higher proportion of unbound T3 (0.30%).

If a change in TBG occurs, the free T4 and T3 concentrations can be maintained at normal levels only if the bound hormone changes in the same direction. For example, if TBG

concentrations are increased by administration of estrogen, the reduction in free T4 lessens T4 clearance, allowing allowing an increase in the plasma total T4 concentration. This is an iterative process that eventually normalizes the free T4 at a new equilibrium without a change in T4 secretion rate.

The most important pathway for T4 metabolism is its outer ring (5') mono deiodination to the active thyroid hormone, T3. This reaction is catalyzed by D1 and D2 and is the source of more than 80% of the circulating T3 in humans. Inner ring deiodination, an inactivating step, is catalyzed primarily by D3, which inactivates T3 and prevents activation of T4 by converting it to rT3 [19,20].

Tissues expressing D3 have lower T3 concentrations than would be expected from the plasma contribution and a gene expression profile similar to that of hypothyroid cells. This is explained by the inactivation of T3 and T4 that takes place

immediately after these hormones enter the cell. The D3-mediated reduction in T3 levels likely occurs in several physiologic settings (e.g., development, regeneration) orpathologic conditions (e.g., cancer cells, inflammation, myocardial infarction) in which D3 is upregulated[21].

Reduced production of thyroid hormone is the central feature of the clinical state termed hypothyroidism[22,23]. Subclinical hypothyroidism is defined as an elevated serum TSH level with a norma serum fT4 concentration[24]. Subclinical hypothyroidism can progress to overt hypothyroidism[25], which is defined as increased TSH with decreased in FT4. Central hypothyroidism is the result of TSH deficiency caused by acquired or congenital hypothalamic or pituitary gland disorders. TSH deficiency caused by pituitary dysfunction is called secondary hypothyroidism, and that of hypothalamic origin is called tertiary hypothyroidism; however, this distinction is not necessary in the initial separation of primary

from central hypothyroidism. Dopamine, dobutamine, high-dose glucocorticoids, and severe illness may suppress TSH release transiently, leading to a pattern of thyroid hormone abnormalities suggesting central hypothyroidism[26].

RELATION BETWEEN THYROID HORMONE AND LIVER:

Liver plays an important role in metabolism of thyroid and gonadal hormoneslike conjugation, excretion, peripheral deiodination, and synthesis of thyroid-binding globulin (TBG) and sex hormone-binding globulin (SHBG)[4-7.] The liver, and to a lesser degree the kidneys, play a dominant, although often under-discussed role in the metabolism of thyroid hormones. The majority of the most metabolically active thyroid hormone, 3,5,3'triiodothyronine(T3), is generated in peripheral tissue. Similarly, the preponderance of its competitive inhibitor, 3,3',5'-triiodothyronine (rT3; reverse

T3) is generated outside the thyroid gland. Further transformations to T2 and T1 isomers also occur almost exclusively in peripheral tissue.

A second pathway of thyroid hormone metabolism involves the conjugation of the phenolic hydroxyl group of the outer phenolic ring with sulfate or glucuronic acid. These conjugation reactions occur primarily in the liver, and to a lesser degree in the kidney, and result in biotransformation of T4 and T3. The resultant metabolites are primed for elimination and are considered relatively inactive.[27] Although T4, T3, and rT3 are generated within the thyroid gland, T4 is quantitatively the major secretory product. All T4 found in circulation is generated in the thyroid unless exogenously administered. Production of T3 and rT3 within the thyroid is relegated to very small quantities and is not considered significant compared to peripheral production[27,28,29] . In peripheral tissues, T4 is either converted to T3 or rT3, or

eliminated by conjugation, deamination, or decarboxylation reactions. It is estimated that more than 70 percent of T4 produced in the thyroid is eventually deiodinated in peripheral tissues, either at the outer phenolic ring to form T3 or at the inner tyrosyl ring to form rT3. T3 is considered to be the most metabolically active thyroid hormone.

Although some T3 is produced in the thyroid, approximately 80-85 percent is generated outside the thyroid, primarily by conversion of T4 in the liver and kidneys[30,31]. Similar to T4, the majority of circulating T3 is in a bound form; however, TBPA and albumin (not TBG) are the binding molecules with highest affinity for T3. The free form of T3 (fT3) found in circulation is more than an order of magnitude greater than fT4, with estimates suggesting fT3 is approximately 8-10 percent of circulating T3[27].

As the liver, and to a lesser extent kidneys, have primary influence on the circulating levels of thyroid hormone metabolites, the health and function of these organs play a critical and under-appreciated role in thyroid hormone function[32].Deiodination of T4 to form T3 or rT3 and the subsequent disposal of rT3 occurs in the liver and kidneys. Available evidencesuggests that, under some circumstances, the activity of hepatic antioxidant enzyme systems and lipid peroxidation might influence the peripheral metabolism of thyroid hormones. Hepatic decarboxylation and deamination enzyme reactions are also capable of influencing the formation and elimination of specific thyroid hormone metabolites.

Currently, three deiodinase families are recognized and are termed isoforms type I, II, and III. These three families differ in terms of their tissue distribution, reaction kinetics, efficiency of substrate utilization, and sensitivity to

inhibitors[33]. Type I deiodinase is the major enzyme in the liver, kidneys, and skeletal muscle; it can carry out both 5'- and 5-deiodination of T4 to produce either T3 or rT3. Type I 5'-deiodinase is a selenium-dependent enzyme, with selenocysteine at the active site of the enzyme; however, type I 5deiodinase enzyme does not require selenium for activity. Type II enzyme is the major deiodinase in the brain, pituitary, and brown adipose tissue. Since tissue equipped with type II isoforms are relatively independent of circulating T3 for their metabolic demands, type II 5'-deiodinase is particularly important for providing the T3 required to stimulate the pituitary to synthesize and secrete TSH. Two Types III deiodinase isoform is also found in the central nervous system and catalyzes the 5-deiodination of T4, resulting in generation of rT3.

In the course of chronic liver disease such as hepatic cirrhosis, alterations in hepatic deiodination resulting in increased rT3

and a simultaneous decrease in T3 levels have also been observed[34].

In animal models, ethanol intake was associated with impaired hepatic 5'deiodination[35].

Among patients with alcohol induced liver cirrhosis, low T3 and T4, elevated rT3, and normal TSH values have been observed[36]. While extreme alcohol-induced liver damage is apparently detrimental to the peripheral modulation of thyroid hormones, it is unclear whether moderate alcohol intake has an impact.

Specific forms of chronic liver disease

In patients with chronic hepatitis associated with primary biliary cirrhosis (PBC) or chronic autoimmune hepatitis, there is an increased prevalence of autoimmune thyroid disease[37,38]. Thus abnormalities may arise from thyroid gland dysfunction or as a consequence of the liver disease.

Autoimmune hypothyroidism is a prominent feature in PBC, occurring in 10–25% of patients[39]. There is often an increase in total T_4 in PBC, due to an increase in thyroid-binding globulin levels, and this may mask hypothyroidism, emphasizing the need to perform a free T_4 and TSH assay. Anti-thyroid microsomal antibodies are common in PBC (34%), as are anti-thyroglobulin antibodies (20%)[40]. Thyroid dysfunction may precede or follow the diagnosis of PBC. In autoimmune hepatitis, both Grave's disease (6%) and autoimmune hypothyroidism (12%) are relatively common[38]. Primary sclerosing cholangitis is associated with an increased incidence of Hashimoto's thyroiditis, Graves's disease and Riedel's thyroiditis[41].

In patients with chronic hepatitis who do not have co-existing autoimmune liver and thyroid disease, total T_4, total T_3, thyroxine-binding globulin levels are often increased, but

TSH and free T_4 levels are usually normal, and patients are clinically euthyroid[8].

Currently the treatment of viral hepatitis with alpha interferon has added another dimension to the abnormalities of thyroid function seen in chronic liver diseases. In different studies assessing patients treated with alpha interferon for hepatitis C, 2.5–10% developed thyroid dysfunction[(42,43)], with both thyrotoxicosis (due to acute thyroiditis) and hypothyoidism being observed. Although the reason is not altogether clear, the induction of an autoimmune reaction has been postulated, resulting in the development of anti-thyroid and anti-thyrotrophin receptor antibodies[44]. However, a distinct effect on intrathyroidal organification of iodine has also been suggested[45]. It should be noted that interferon therapy causes weakness and muscle aching, and in this setting the myopathy of hypothyroidism may be missed. It is therefore

recommended that thyroid function tests (including thyroid antibodies) are performed prior to therapy, and subsequently monitored at 3–6 month intervals during interferon therapy[46].

In chronic hepatitis B, predominantly a disease of males, the frequency of pre-treatment thyroid antibodies and the induction of thyroid antibodies and thyroid dysfunction during interferon therapy, are all lower than in chronic hepatitis C[47].

Overall, the majority of patients with liver disease are clinically euthyroid, and this can be confirmed with a normal high sensitivity TSH test and a normal free T_4. The latter test is routinely performed and obviates the need to take into account the variation in thyroid-binding globulin levels seen in patients with liver disease.

Assessment of thyroid and gonadal function in liver diseases was conducted on about 75 patients by Sandeep kharb et al[(48)] with acute hepatitis (AH), chronic liver disease (CLD), and

those who had undergone liver transplantation (LT). Patients with chronic liver disease further subdivided according to child pugh score which includes CLD-1(CTP A) and CLD-2(CTP B and C).Thyroid dysfunction was noted in 14 patients(16%) of patients with liver disease. Among thyroid dysfunction, the commonest was sick euthyroid syndrome six (7%), followed by subclinical hypothyroidism in three patients (3.5%), subclinical hyperthyroidism and thyrotoxicosis in two patients each (2.3%) and overt hypothyroidism in one patient. Among patients with LT and AH groups, the only abnormality was significantly lower total T3 compared with healthy controls. The CLD2 group had significantly lower levels of all thyroid hormones compared with controls and CLD1 group.

Indian study conducted by G.Deepika et a,[49] on about 310 cirrhotic patients aged 20-80years, to find out Prevalence of hypothyroidism in Liver Cirrhosis among Indian patients.

Both genders were included .Male are 211 and Female are 99. The control group comprised randomly selected non cirrhosis subjects. The total number of control subjects is 250 aged 20-80 years. Male are 145 and female are 105. The result showed that there was a significantly increased between cirrhotic patients and non-cirrhotic subjects for TSH and slightly decreased T3 andT4 where the p value is 0.039, 0.014 and 0.245 respectively. The mean of TSH levels of cirrhotic patients is higher than the mean of non-cirrhotic subjects and show significant difference. And also there is significant difference for T3 between two groups, but T4 seems no significant difference between two groups.

A study conducted by K.V.S.Harikumar et al[50] on occult endocrine dysfunction in patients with cirrhosis of liver consists of 30 patients which shows that 30% of patients were found to be thyroid dysfunction. That include subclinical hypothyroidism (n = 3), primary hypothyroidism (n = 1), Sick

Euthyroid syndrome (n = 3), central hypothyroidism (n = 2) and secondary hypogonadism (n = 3). But none of the results was statistically significant individually. But considering hypothyroidism as a single entity which includes all subtypes, it was found out to be statistically significant.

Serum Level of Thyroid Hormones in Patients with Chronic Hepatitis C Virus Infection by Mohamed Abdel-Fattah El-Feki et al[51] on about 60 patients with CHC infection were selected for the study. They were divided into two groups: with or without liver cirrhosis. Those with liver cirrhosis were further subdivided according to the Child-Turcotte-Pugh scoring system. Serum levels of free T3 (FT3), free T4 (FT4) and TSH were measured to all patients. Results shown that there was decrease in the FT3 and FT4 levels and increase in the TSH levels in patients with CHC with cirrhosis when compared to patients with CHC without cirrhosis. This study concludes that thyroid profile abnormalities were seen in

cirrhotic HCV patients when compared to non-cirrhotic patients. The abnormalities in the serum level of THs (decreased FT3, FT4, and increased TSH) are strongly associated with the severity of liver damage and advancing of the child score.

Oren R et al[52] conducted a reterospective study on hypothyroid versus the euthyroid state, a significant negative correlation was found between thyroid-stimulating hormone blood levels and both functional and synthetic liver function tests ($p < 0.001$). A significant negative correlation was also found between thyroid-stimulating hormone blood levels and clinical deterioration manifested as bleeding varices, the development of ascites, and episodes of encephalopathy. We conclude that in patients with liver cirrhosis, the liver function in the hypothyroid state tend to be better than in the euthyroid state. A mild controlled decreased thyroid function may be beneficial for euthyroid cirrhotic patients.

Takahashi1 et al[53] conducted a study on changes of thyroid hormones in various liver diseases: usefulness of free thyroid hormones as liver function test. Various thyroid parameters in liver disease which were morphologically diagnosed were measured, and their relationship to liver function was mainly studied. Serum T4 levels were elevated in acute hepatitis (AH), chronic persistent hepatitis (CPH) and chronic aggressive hepatitis (CAH)compared with in normal controls (C). Serum T3 levels were elevated in CAH and reduced in liver cirrhosis (LC). Serum reverse T3 (rT3) levels were elevated in AH and chronic liver diseases (CLD). T3/T4 ratios decreased in AH, CPH and CAH. RT3/T3 ratios increased in AH and CLD. Serum Free T3 (FT3) levels reduced in CLD in order of CPH, CAH and LC, and were low levels in AH with the same degree as LC. Moreover, serum FT3 levels positive correlation with prothrombin time (PT) and serum albumin levels (Alb). Therefore serum FT3 level was considered to

become a sensitive index of liver damage. Serum free T4 (FT4) levels did not change significantly in AH with high levels of transaminases and reduced in only LC. Therefore serum FT4 may become an index of severity of liver dysfunction. On the other hand, T3/T4 ratios and rT3/T3 ratios showed less correlation with liver function tests compared with free thyroid hormones.

M Borzio et al[8] evaluate thyroid function in patients with liver disease, they measured total and free T3 and T4, thyroxine binding globulin, basal and thyrotropin releasing hormone-stimulated thyrotropin and thyroglobulin antibodies in 33 patients with liver cirrhosis, T3, FT3 and T3/thyroxine binding globulin and thyrotropin after thyrotropin releasing hormone were significantly reduced.

The study conducted on Serum Thyroid Hormone Levels in Sudanese Patients with Liver Cirrhosis by Hussein Awad

Mousa et al[54] The study revealed significant decrease level of T3 (p value <0.05) in cirrhotic patients than controls, while TSH and T4 were insignificantly changed. It also appears that there was no significant correlation between duration of cirrhosis and thyroid hormones among cirrhotic patients.

Fariborz Mansour-Ghanaei et al[55] conducted a study on Thyroid hormones profile in patients with hepatic cirrhosis due to chronic HBV and HCV infections was evaluated in order to find any relationship between thyroid hormones and severity of liver damage. Patients with the diagnosis of hepatic cirrhosis due to hepatitis B or C were screened for thyroid function status. Child-Pugh and model for end-stage liver disease (MELD) scores were calculated. Considering each thyroid function test, patients were divided into two groups with lower than normal and normal range of thyroid hormones, separately for each (for TSH, normal and upper than normal). The correlation between thyroid function tests

and severity of liver disease was taken into account. Number of patients with a T3 level lower than normal range (70-110 ng/dL) significantly increased along with Child-Pugh scores A, B and C. A negative correlation was found between Child-Pugh scores and total serum T3 level ($r = -0.453$, $P < 0.001$). Also a reverse correlation was observed between MELD score and T3 levels ($r = -0.305$, $P = 0.14$). Study concluded that serum T3 concentration is a good index of hepatic function, decreasing by the severity of liver damage.

Sanul A et al[56], studied conducted a study on 55 patients with liver cirrhosis and compared with 78 controls concluded that The mean serum concentration of T3, FT3 and FT4 were significantly decreased in cirrhotics, while no significant change was noted in serum T4 and TSH levels. T3/T4 ratio was also lower than the normal. This indicates an impaired liver conversion of T4 to T3 in peripheral tissues. Serum T3

and FT3 showed an inverse correlation with serum bilirubin and a positive correlation with serum albumin.

Summary and perspectives:

The liver is a major site of peripheral conversion, degradation and excretion of thyroid hormones. Therefore, abnormal thyroid function at all levels of hypothalamic-pitutary-thyroid axis is expected in patients with liver cirrhosis[57].

Several abnormal alterations in the thyroid gland have been identified in patients with cirrhosis, these ranges from alterations in thyroid size, morphology and architectural pattern to alteration in thyroid hormone metabolism and regulation.

The volume of the thyroid gland is reported to increase by upto 17% in cirrhosis patients compared with non-cirrhotic controls, as measured using ultrasonography[58]. The prevalence of thyroid hormone abnormality ranged from 13%

to 61%. In patients with cirrhosis, hypothyroidism was more frequently seen, and hyperthyroidism has also been reported[59]. The most consistent thyroid hormone profile in patient with cirrhosis is low total and free T3 and elevated rT3 levels, similar to changes in patients with sick euthyroid syndrome. This results in a decrease in conversion of T4 to T3. The T3:Rt3 ratio parameter of liver function[60,61,62-66].

Regarding the association between severity of cirrhosis and thyroid function, low T4 levels may be related with decreased short and long term survival of patient with liver cirrhosis[61]. Low T3 levels are a good indicator of disease severity in cirrhosis[67].A negative correlation was found between child-pugh scores and total serum T3 levels[55].

Low total and free T3 levels may be considered an adaptive condition that contribute toreducing the basal metabolic rate within hepatocytes to preserve liver function. Indeed, recent

study showed a significant improvement of liver function, including alanine aminotransferase, alkaline phosphate, albumin, bilirubin and prothrombin time in patients with increased TSH.

Also in case of stable cirrhosis, a hypothyroidism has been shown which correlates with slow progression of stage of cirrhosis[68,52]. Therefore thyroid dysfunction may disturb liver functions and liver diseases modulate thyroid hormones metabolism[5].However further studies are required to test this hypothesis. As thyroid hormone disorders are prevalent in liver cirrhosis, awareness of thyroid function in liver disease is necessary.

AIMS AND OBJECTIVES

1. To study the occurrence of hypothyroidism in patients with chronic liver disease.

2. To study the relationship between serum FT3 and child-pugh score.

MATERIALS AND METHODS

INCLUSION CRITERIA:

-Patients with age >18years, either sex with evidence of chronic liver disease.

EXCLUSION CRITERIA:

1. -known case of hypothyroidism on treatment
2. -Pregnant female
3. -Medications that affect study like phenytoin, amiodarone, NSAIDS, Salicylates.
4. - Patients with sepsis

STUDY DESIGN: Cross sectional observational study

STUDY PERIOD: september 2016 to september 2017

STUDY PLACE: Dept. of Medicine, kanyakumari government medical college.

SAMPLE SIZE: Minimum 50 cases

CONTROL: 50 age, sex matched controls from hospital health care group personnel.

METHODOLOGY

*Patients of chronic liver are selected for our study on the basis of:

*Duration of disease greater than 6 months

In practical clinical terms diagnosis of chronic liver disease is made in the presence of duration >6 months[11]. Cirrhosis, a final pathway for a wide variety of chronic liver diseases, a combination of clinical(signs and symptoms of liver cell failure), laboratory (raised bilirubin, SGOT, SGPT, low albumin), and imaging features (absence of thin hyper echoic line, paucity of peripheral hepatic vessels, accentuated echogenic walls of the portal vein, nodular liver cirrhosis, contracted, signs of portal hypertension) can help to confirm the diagnosis[12].

* Child pugh score >6. Child pugh score was calculated according to the table

As most of the in and out patients presents to our hospital in later stages of disease so cases belongs to CTP B and C are included in the study and compared.

MEASURE	1 POINT	2 POINTS	3 POINTS
Total bilirubin µmol/l(mg/dl)	<34(<2)	34-50(2-3)	>50(>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4

*USG findings suggestive of chronic liver disease like-

- Nodular irregular surface of liver
- Distorted vascular pattern
- Ascites
- Signs of portal hypertension (splenomegaly or dilated portal venous system on ultrasonography)

* Evidence of esophageal varices on upper gastro intestinal endoscopy.

1. All patients will undergo a detailed clinical examination at admission. Relevant history and physical examination including symptom and signs of liver failure, hepatomegaly, splenomegaly and abdominal vein collaterals will be recorded. Ascites will be graded as none, mild, moderate and severe.
2. Haematological and biochemical workup will include measurement of haemoglobin, total leucocyte count, platelet count, prothrombin time and serum concentration of bilirubin (both direct and indirect), protein , albumin, alanine aminotransferase and aspartate aminotransferase. For each patient a child pugh score will be calculated [(69)].

3.Ultrasonography

All patients will undergo ultrasonography after overnight fast and the following details will be recorded: Maximum vertical span of liver; nodularity of liver surface; spleen size (length of its axis); diameter of portal and splenic veins ;presence of portal-systemic collaterals; and presence of ascites.

4.Hormonal assessment

Blood tests are currently the most accurate way to diagnose thyroid disorders. Fasting venous sample taken in the vaccutainer in the early morning is the best method to test thyroid hormones level[(70)].

FT3 and FT4 - Free T3 and FT4 tests will be performed using the VITROS free T3 and free T4 reagent pack and the VITROS free T3 and free T4 calibrators on the VITROS ECi/ECiQ Immunodiagnostic system.

TSH

TSH levels are determined by VITROS TSH test. VITROS TSH test is performed using the VITROS TSH Reagent and system using Intellicheck technology. An immediate immunoassay technique is used, which involves the simultaneous reaction of TSH present in the sample.

The normal values of the thyroid function test were taken as the following according to the bio-chemistry laboratory. Kanyakumari government medical college , where the evaluation was carried out.

TSH----→ 0.5-5.0IU/ml

FT3-----→2.0-4.4pg/dl

FT4----→0.6-2.2ng/dl

STATISTICAL ANALYSIS

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-

1.Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.

2.Qualitative variables were correlated using Chi-Square test /Fisher's exact test.

3. Spearman rank correlation coefficient was used to assess the association of CTP score with various parameters.

A P value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

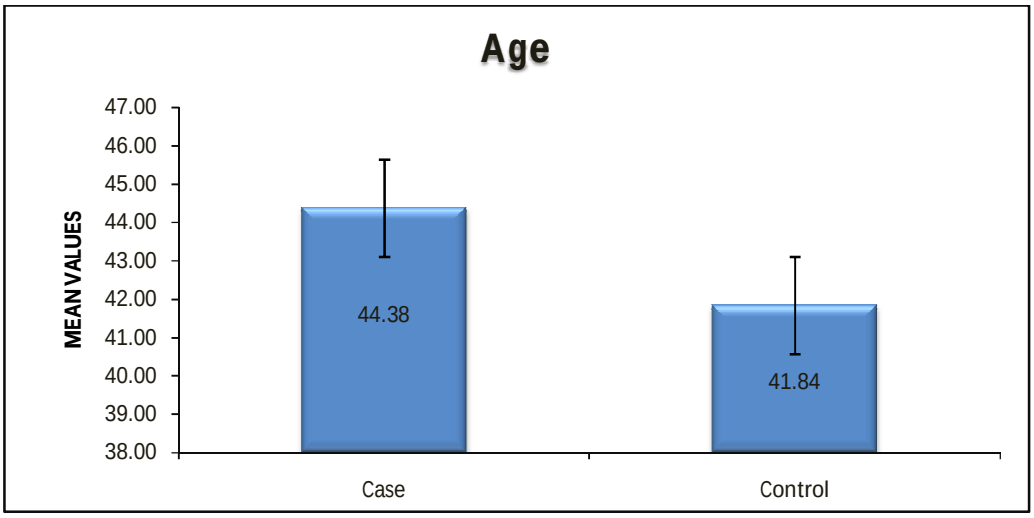
OBSERVATION AND RESULTS

A total of 50 patients with chronic liver disease were enrolled in the study and 50 age and sex matched healthy controls were controlled.

1.Patient characteristics

Table 1-Age Distribution Among studyGroups-

	Case	Control
	Mean±Stdev	Mean±Stdev
	44.38±9.33	41.84±8.24



Thus, cases showed a mean age of 44.38±9.33 and controls a mean age of 41.84±8.24. There was no significant difference between age of cases and controls.

Table 2-Age grouping

		Group		Total	P value	
		Case	Control			
Age distribution	1)<=30	6(12.00%)	6(12%)	12(12%)	0.299	
	2)31-40	10(20%)	15(30%)	25(25%)		
	3)41-50	21(42%)	23(46%)	44(44%)		
	4)>50	12(26%)	6(12%)	6(6%)		
		50(100%)	50(100%)	100(100%)		

Figure 2-Age grouping

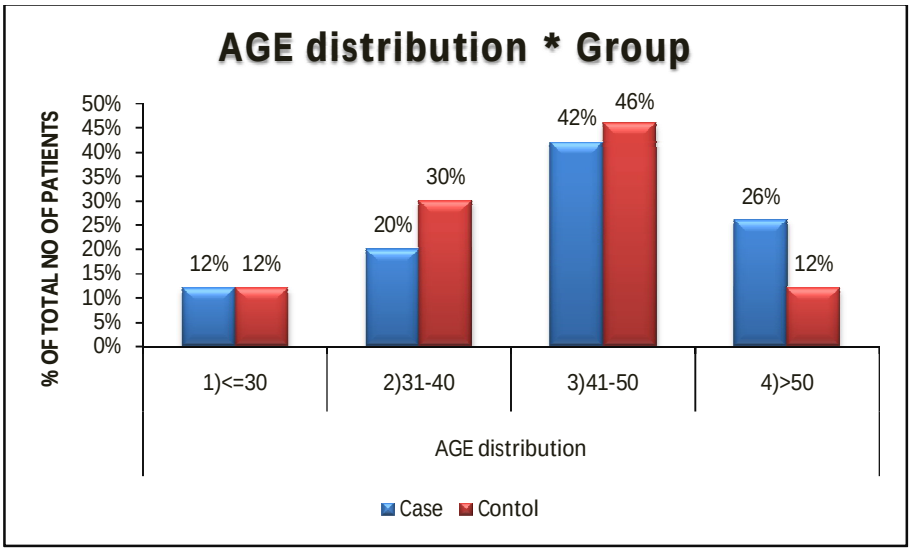
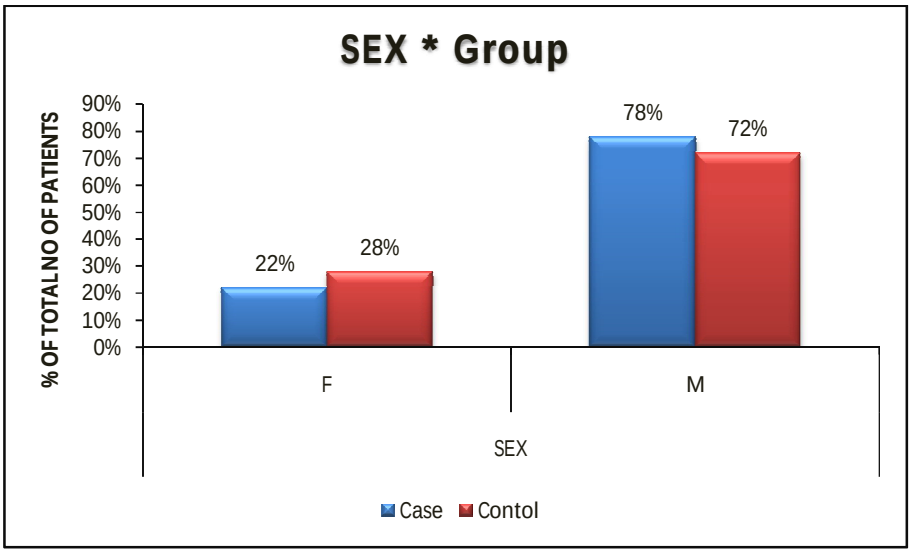


Table 3-Sex Distribution Among study group-

		Group		Total	P value
		Case	Control		
Sex	Female	11(22%)	14(28%)	25(25%)	0.488
	Male	39(78%)	36(72%)	75(75%)	
Total		50(100%)	50(100%)	100(100%)	

Figure 3-Sex Distribution Among study group2%

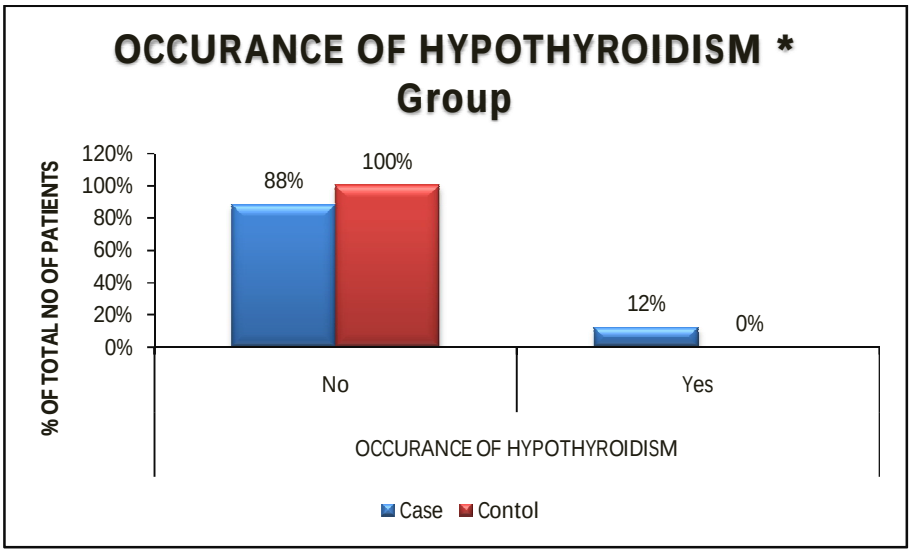


Thus, out of 50 cases 39(78%) are males and 11(22%) are females. Out of 50 persons in control group 36(72%) males and 14(28%) are females.

Table 4- Hypothyroidism distribution

		Group		Total	P value
		Case	Control		
Occurance of hypothyroidism	No	44(88%)	50(100%)	94(%)	0.027
	Yes	6(12%)	0(0.00%)	6(6%)	
Total		50(100%)	50(100%)	100(100%)	

Figure 4-hypothyroidism distribution

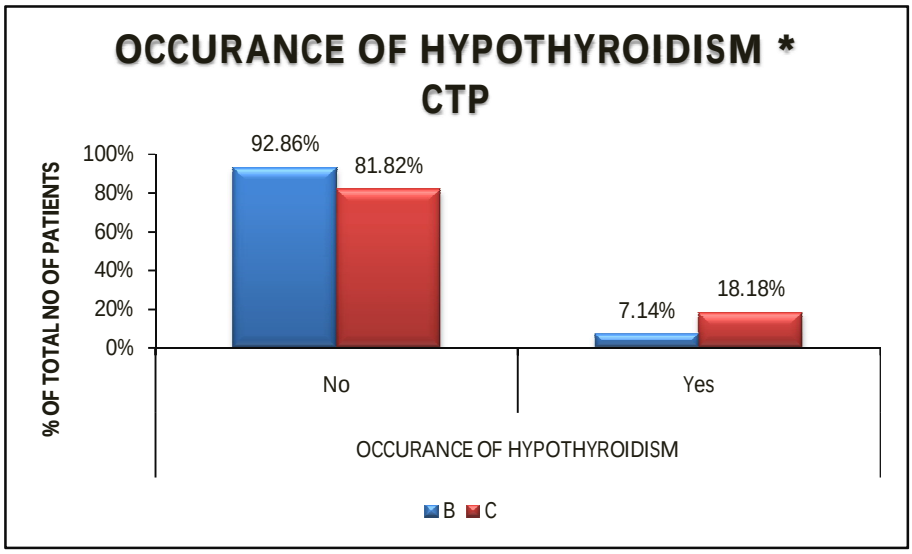


Thus this study shows hypothyroidism is present in 6(12%) patients with chronic liver disease with a statically significant p value of 0.027.

Table 5- Distribution of Hypothyroidism in different child-pugh score

		CTP		Total
		B	C	
Occurrence of hypothyroidism	No	92.86%	81.82%	88%
	Yes	7.14%	18.18%	12%
Total		100%	100%	100%

Figure 5-Distribution of Hypothyroidism in different Child-pugh score

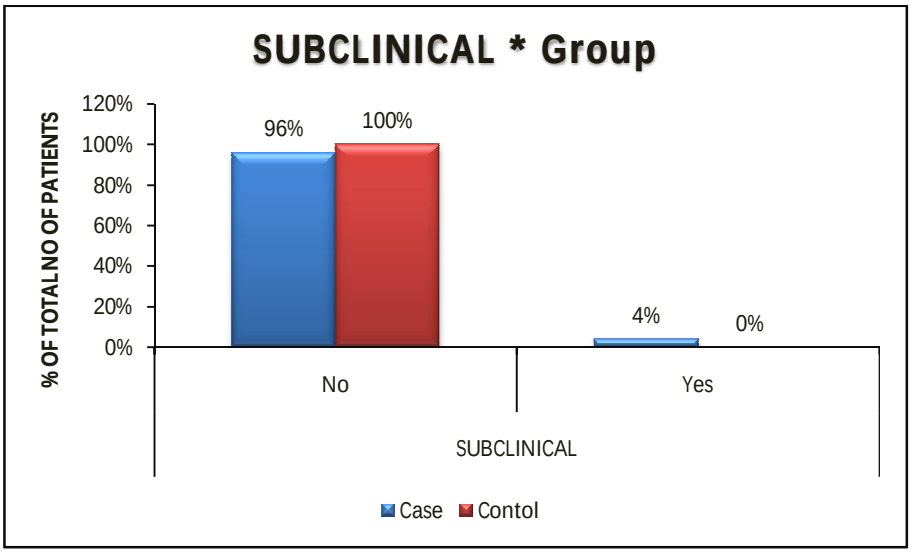


Out of 28 patients belongs to child-pugh score B 2(7.14%) patients are found out to be Hypothyroidism. 4(18.8%) out of 22 patients in child-pugh C are found to be hypothyroidism.

Table –6: Subclinical hypothyroidism among study group

		Group		Total	P value
		Case	Control		
Subclinical hypothyroidism	No	48(96%)	50(100%)	98(98%)	0.495
	Yes	2(4%)	0(0.00%)	2(2%)	
Total		50(50%)	50(100%)	100(100%)	

Figure-6: subclinical hypothyroidism among study group

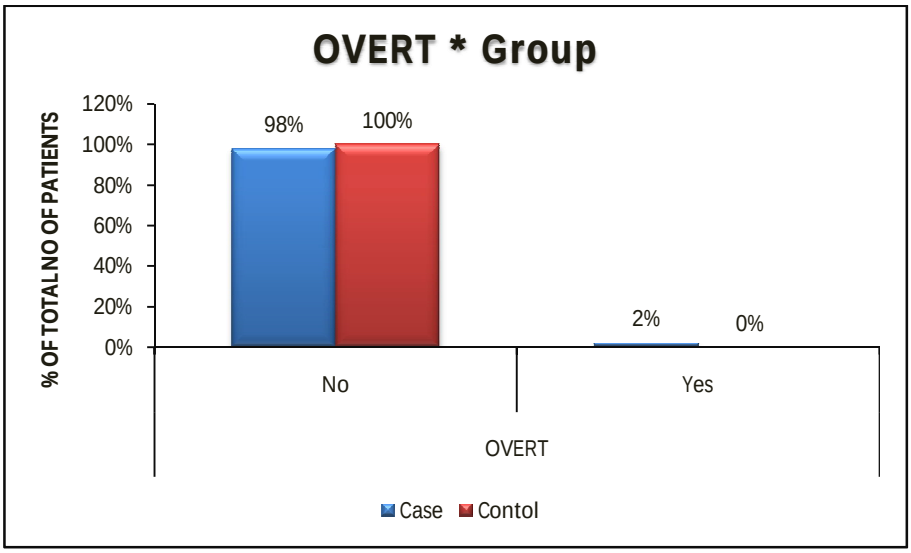


Thus this study shows that out of 50 cases subclinical hypothyroidism is present in 2(4%) patients with chronic liver disease with statistically insignificant P value of 0.495.

Table 7-Overt hypothyroidism in study group

		Group		Total	P value
		Case	Control		
Overt hypothyroidism	No	49(98%)	50(100%)	99(99%)	1.000
	Yes	1(2%)	0(0.00%)	1(1%)	
		50(100%)	50(100%)	100(100%)	

Figure 7-Overt hypothyroidism in study group

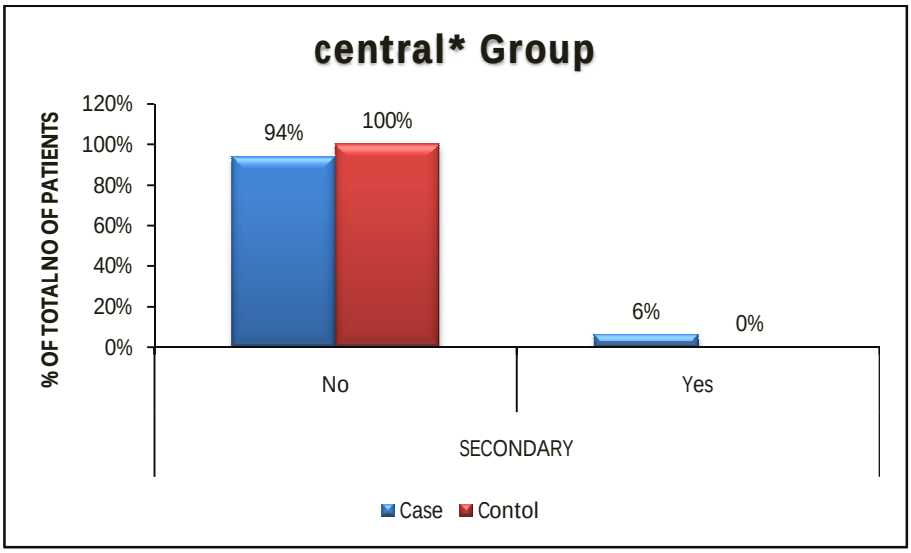


This study shows that out of 50 cases, overt hypothyroidism is present in 1(2%) patient with chronic liver disease with statistically insignificant P value of 1.00

Table 8-central hypothyroidism among study groups

		Group		Total	P value
		Case	Control		
Central hypothyroidism	No	47(94%)	50(100%)	97(97%)	0.242
	Yes	6(6%)	0(0.00%)	3(3%)	
Total		50(100%)	50(100%)	100(100%)	

Table-8-central hypothyroidism among study groups

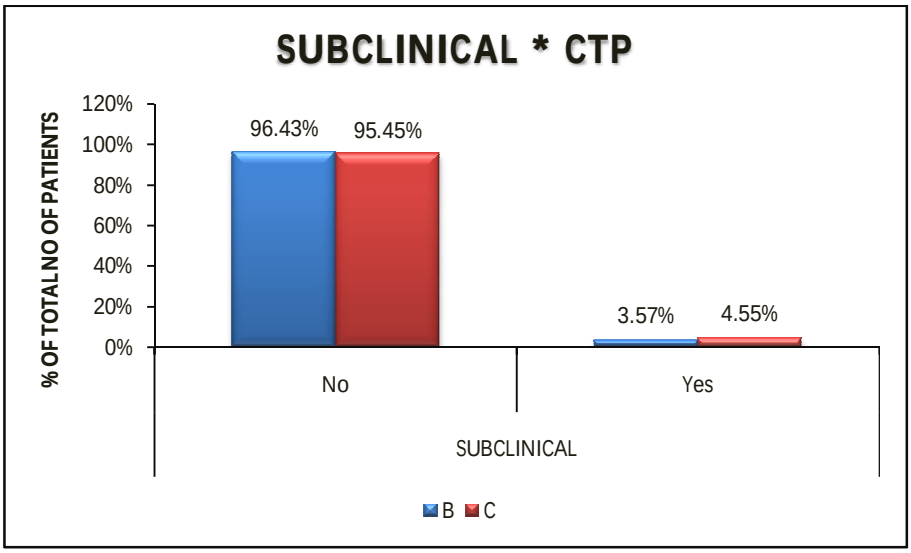


Central hypothyroidism is present in 3(6%) out of 50 patients in our study with insignificant p value of 0.242

Table 9-subclincal hypothyroidism with CTP

		CTP		Total
		B	C	
Subclinical hypothyroidism	No	96.43%	95.45%	96.00%
	Yes	3.57%	4.55%	4%
Total		100%	100%	100%

Figure 9-subclinical hypothyroidism with CTP

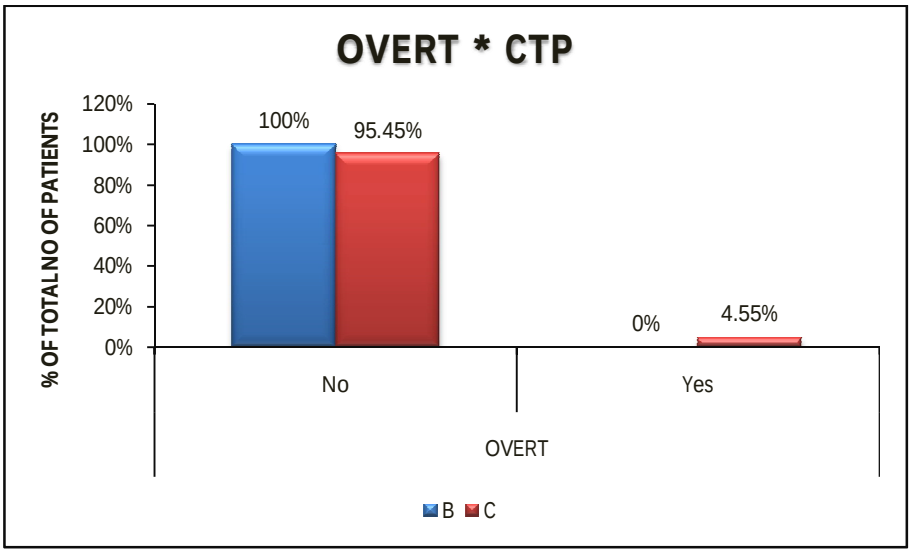


1(3.57%) out of 28 patients in Child-pugh B and 1(4.55%) out of 22 patients with CTP C are found to be subclinical hypothyroidism

Table 10-overt hypothyroidism with CTP

		CTP		Total
		B	C	
Overt hypothyroidism	No	100%	95.45%	98%
	Yes	0.00%	4.55%	2%
Total		100%	100%	100%

Figure 10-overt hypothyroidsm with CTP

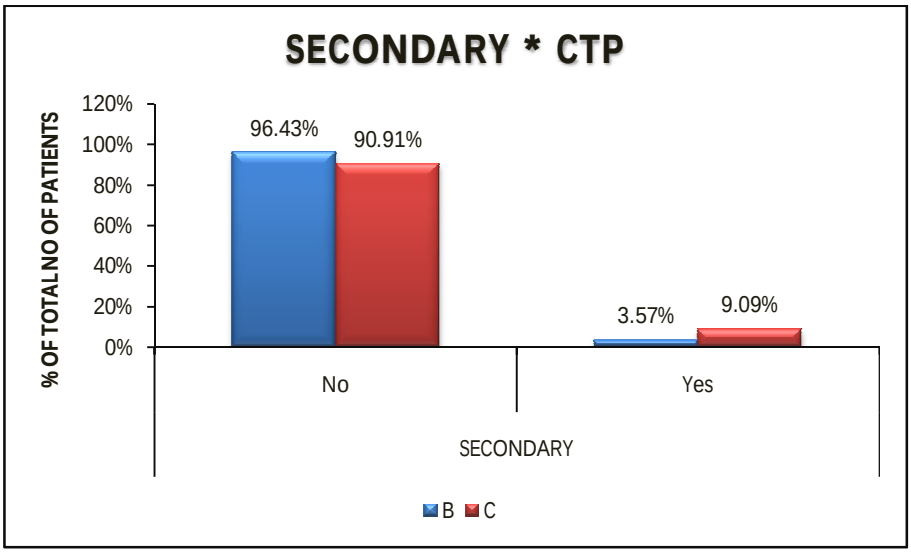


1(4.55%) out of 22 patients with CTP C is overt hypothyroidism but none in CTP B is belongs to this category.

Table – 11 Central hypothyroidism with CTP score

		CTP		Total
		B	C	
Secondary hypotjyroidism	No	96.43%	90.91%	94.00%
	Yes	3.57%	9.09%	6.00%
Total		100%	100%	100%

Figure -11 central hypothyroidism with CTP score

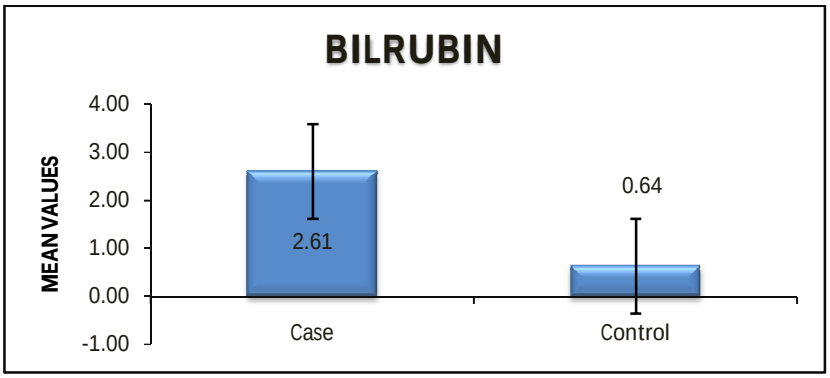


1(3.57%) out of 28 in CTP B and 2(9.09%) out of 22 patients in CTP C are found to be secondary hypothyroidism

Table 12-Bilrubin among study group

Bilrubin	Case	Control	P value
Sample size	50	50	
Mean±Stdev	2.61±1.12	0.64±0.22	<0.001
Median	2.3	0.6	
Min-Max	0.6-6.9	0.2-1.1	
Interquartile range	1.900-3.100	0.500-0.800	

Table 12-Bilrubin among study group

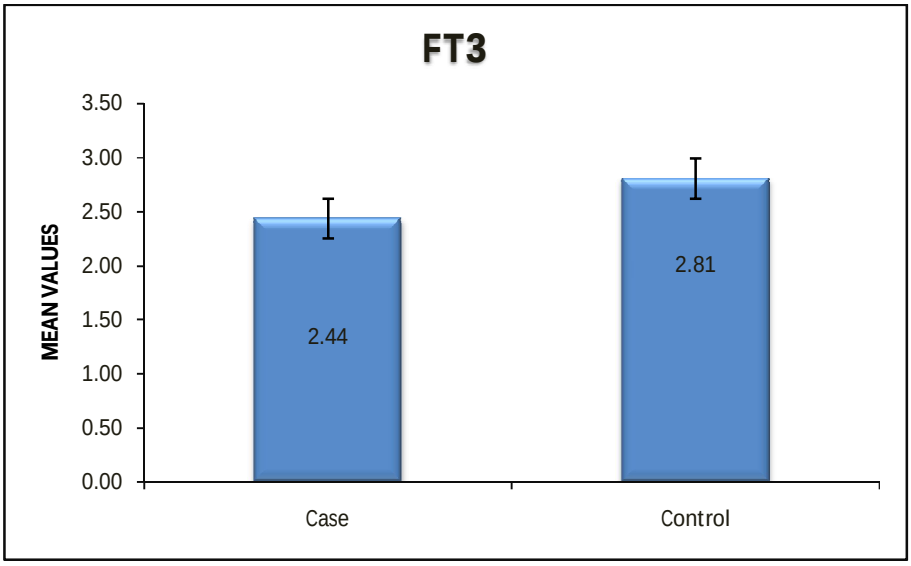


Thus**,** bilrubin is significantly higher in case group with a mean 2.3mg/dl as compared to control group with a mean of 0.6mg/dl.Pvalue is <0.001

Table 13-FT3 among study groups

	Case	Control	P value
Sample size	50	50	0.001
Mean±Stdev	2.44±0.72	2.81±0.52	
Median	2.27	2.84	
Min-Max	1.41-4.2	1.78-4	
Interquartile range	1.910-2.810	2.450-3.100	

Figure 13-FT3 among study groups

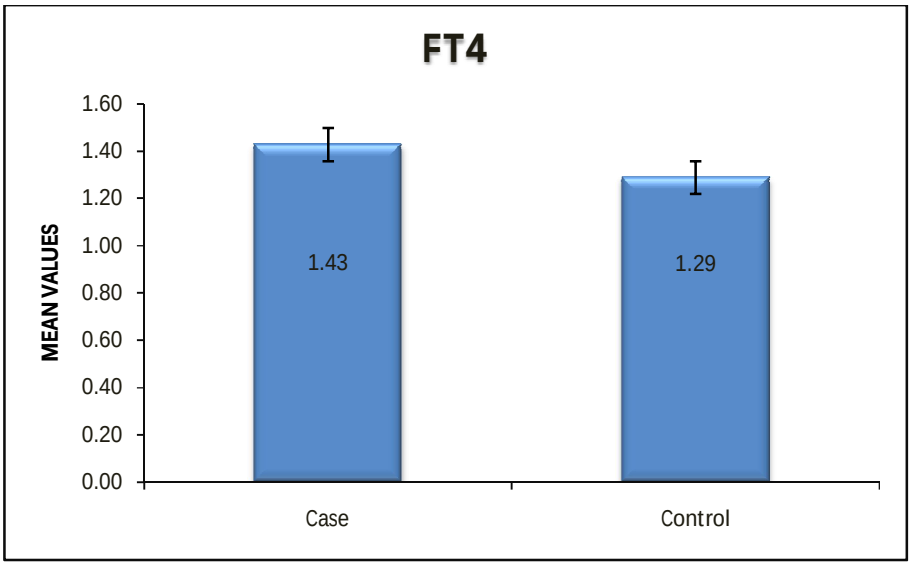


Thus, FT3 is significantly lower in case groups with a mean of 2.44 as compared to control group with a mean of 2.81and it s found to be statistically significant with P value of 0.001

Table 14-FT4 among study groups

	Case	Control	P value
Sample size	50	50	
Mean ± St dev	1.43±0.61	1.29±0.42	0.285
Median	1.34	1.1	
Min-Max	0.41-3.04	0.74-2.17	
Interquartile range	0.960-1.860	1.020=1.550	

Figure 14-FT4 among study group

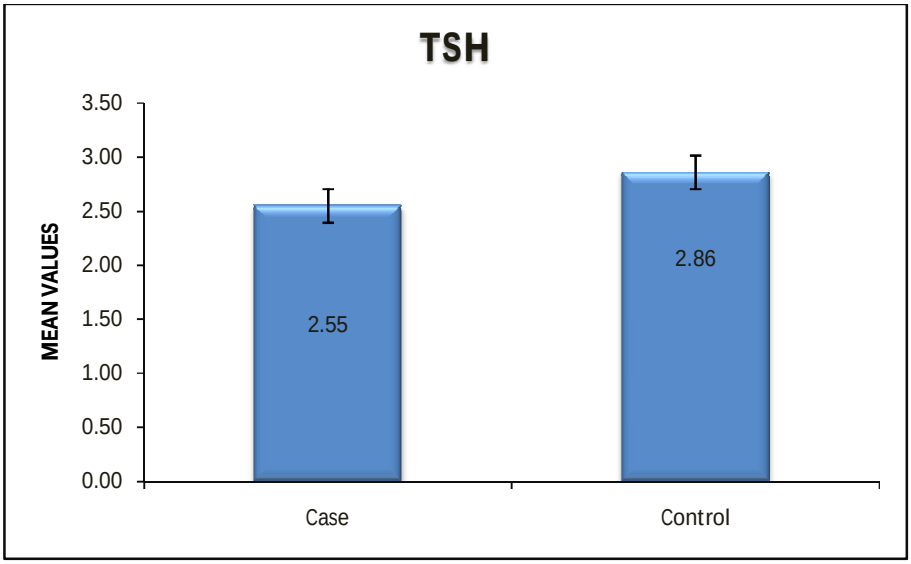


Thus,FT4 is higher in case group with a mean of 1.43 compared to control with a mean of 1.29 and it is statistically insignificant.

Table -15 TSH among study groups

	Case	Control	P value
Sample size	50	50	
Mean ± St dev	2.55±2.57	2.86±0.89	0.008
Median	2.09	2.94	
Min-Max	0.13-14.7	1.38-4.48	
Interquartile range	0.780-3.200	2.060-3.470	

Figure 15- TSH distribution among study groups

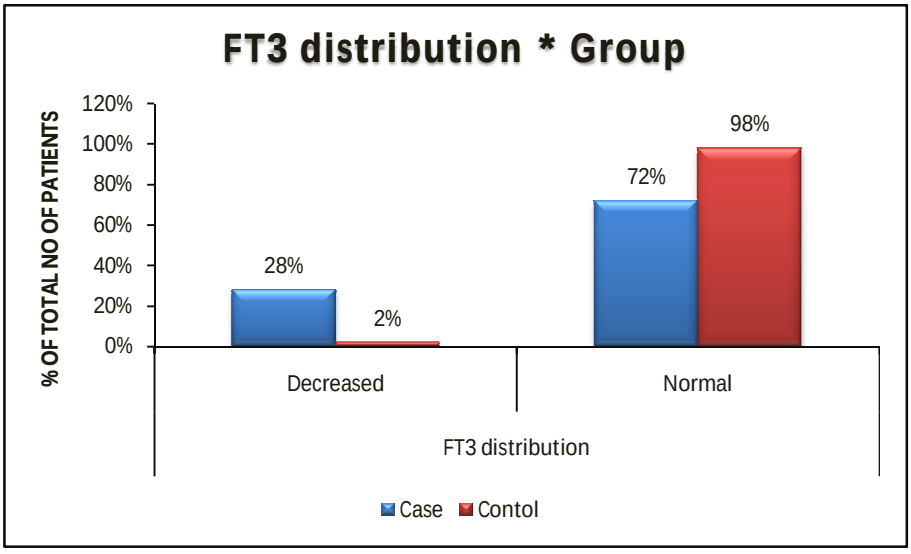


Thus,TSH is significantly lower in case group with a mean of 2.55 as compared to control group with a mean of 2.86 and it is found to be statistically significant.

Table 16-FT3 distribution among study groups

		Group		Total	P value
		Case	Control		
FT3 distribution	Decreased	14(28%)	1(2%)	15(15%)	0.0004
	Normal	36(72%)	49(98%)	85(85%)	
Total		50(100%)	50(100%)	100(100%)	

Figure 16-FT3 distribution among study groups

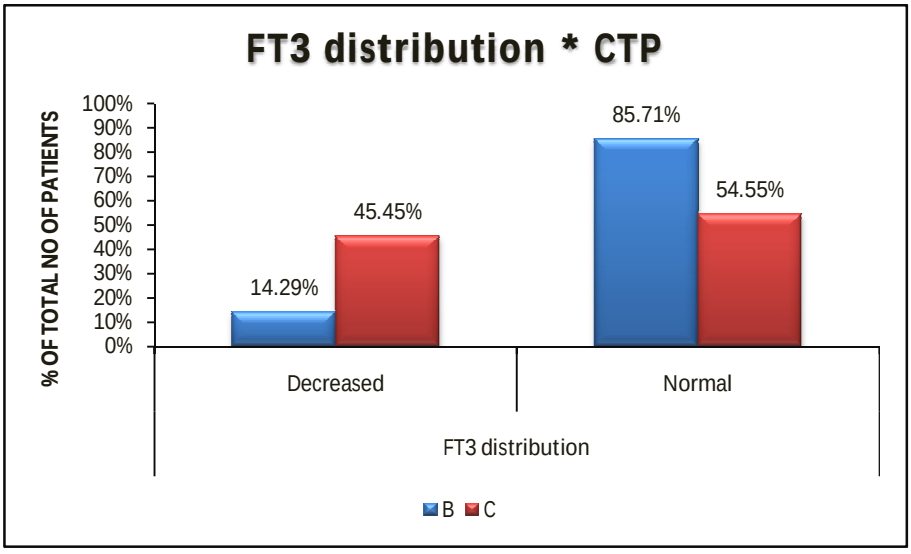


FT3 is found to be decreased in 14(28%) patients out of 50. 1(2%) out of 50 controls found to be low FT3. P value is found to be 0.0004

Table 17-FT3 distribution with child pugh score

		CTP		Total	P value
		B	C		
FT3 distribution	Decreased	4(14.29%)	10(45.45%)	14(28%)	0.025
	Normal	24(85.71%)	12(54.55%)	36(72%)	
Total		28(100%)	22(100%)	50(100%)	

Figure 17-FT3 distribution with child pugh score

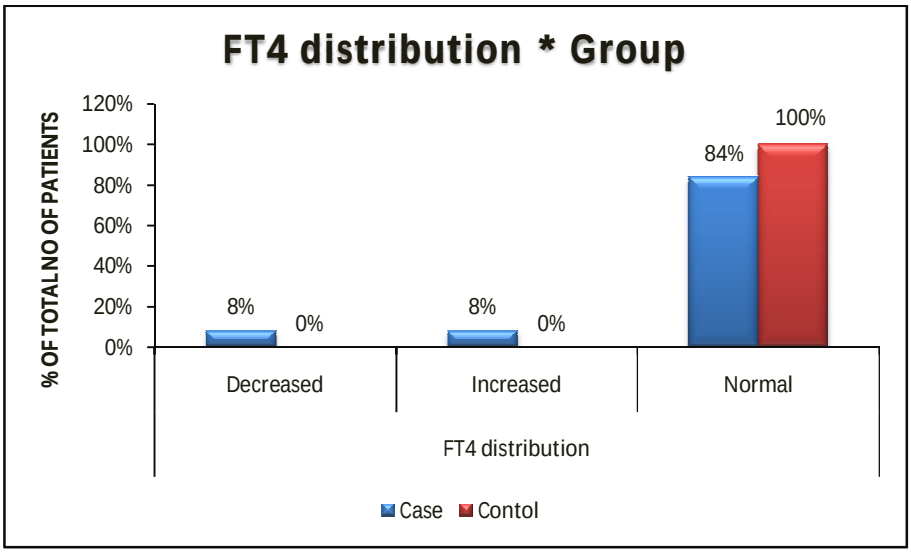


Among 28 patients in child pugh B FT4 is found to be decreased in 4(14.29%) patients. Out of 22 patients in child pugh C FT3 is found to be decreased in 10(45.45%) patients.

Table 18-FT4 distribution among study groups

		Group		Total	P value
		Case	Control		
FT4 distribution	Decreased	4(8%)	0(0.00%)	4(4.00%)	0.013
	Increased	4(8%)	0(0.00%)	4(4.00%)	
	Normal	42(84%)	50(100%)	92(92%)	
Total		50(100%)	50(100%)	100(100%)	

Figure 18-FT4 distribution among study groups

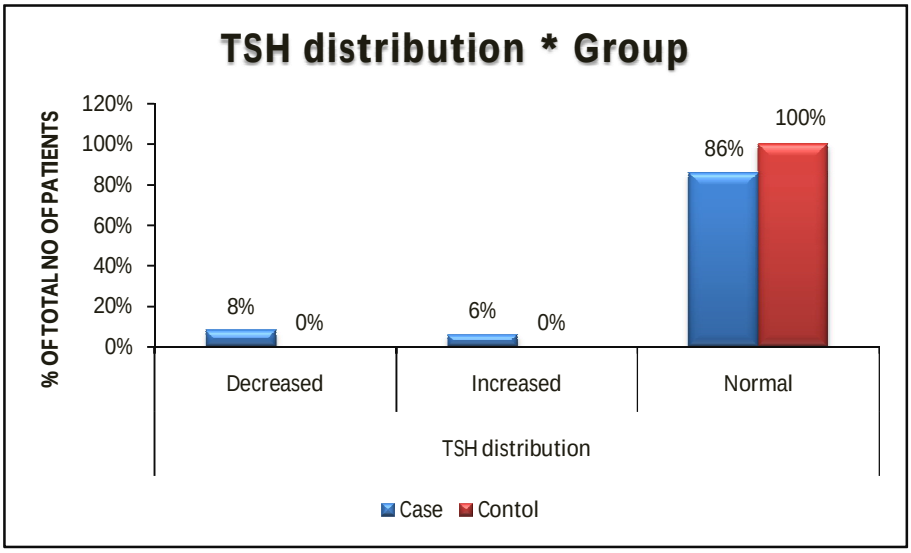


Out of 50 cases 4(8%) patients are found to be increased and 4(8%) patients are found to be decreased FT4. None of the controls shows any variation. P value is found to be statistically significant of 0.013

Table 19: TSH distribution among study groups

		Group		Total	P value
		Case	Control		
TSH distribution	Decreased	4(8%)	0(0.00%)	4(4%)	0.023
	Increased	3(6%)	0(0.00%)	3(3%)	
	Normal	43(86%)	50(100%)	93(93%)	
Total		50(100%)	50(100%)	100(100%)	

Figure 19:TSH distribution among study groups

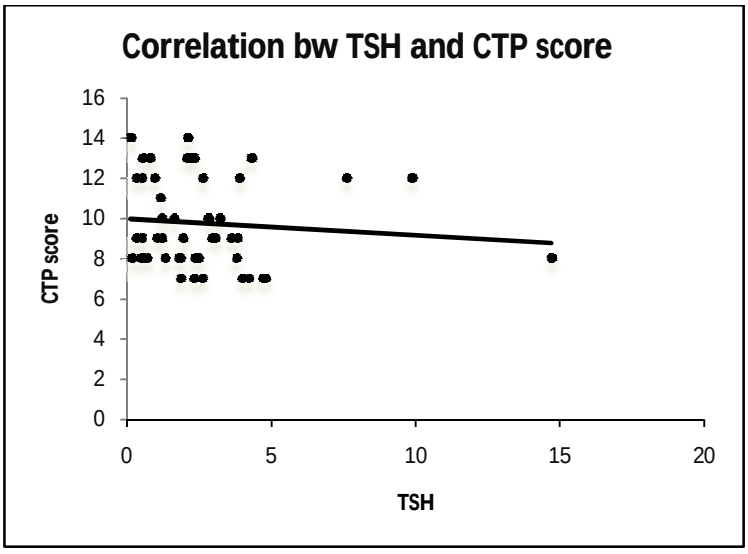


TSH levels found to be decreased in 4(8%) and increased in 3(6%) out of 50 cases. None of the controls shows any variation. P value is found to be stastistically significant.

Table 19:Correlation between TSH and child-pugh score

TSH	Correlation co-efficient	-0.176
	P value	0.2224
	Sample size	50

Figure 19:Correlation between TSH and Child-pugh score

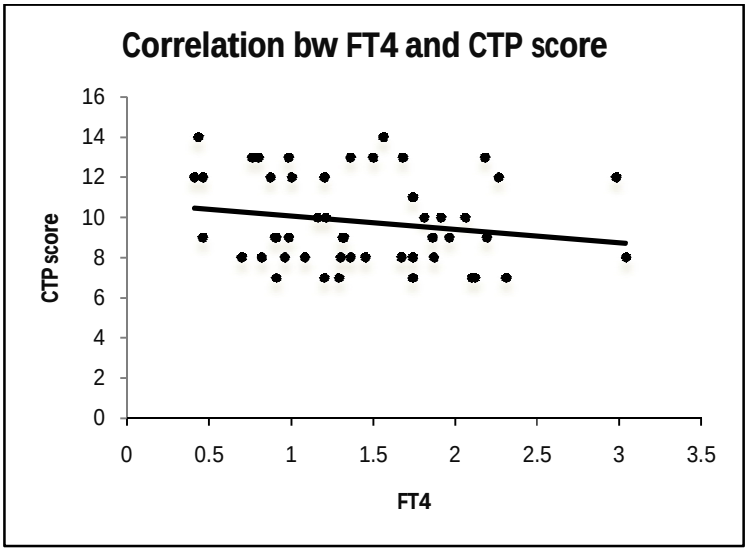


TSH is found to be negatively correlated with Child-pugh score with correlation co-efficient of -0.176 but it is found to be statistically insignificant with P value of 0.2224

Table 20: Correlation between FT4 and Child-pugh score

FT4	Correlation co-efficient	-0.191
	P value	0.1849
	Sample size	50

Figure 20: Correlation between FT4 and Child-pugh score

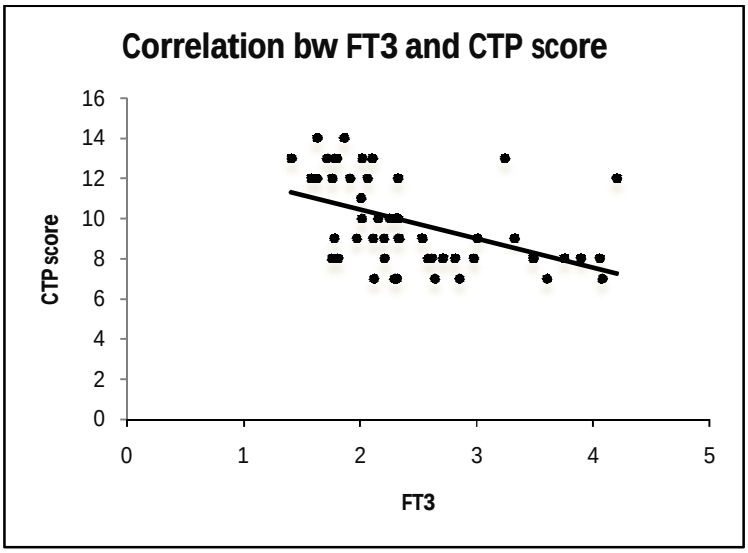


FT4 is found to be negatively correlated with Child-pugh score with correlation co-efficient of -0.191 which is statistically insignificant P value of 0.1849

Correlation between FT3 and Child-pugh score:

FT3	Correlation Coefficient	-0.57
	Significance Level P	<0.001
	Sample size	50

Correlation between FT3 and Child-pugh score:



FT3 is found to be negatively correlated with Child-pugh score with correlation co-efficient of -0.57 and P value of 0.001

DISCUSSION

In our study 50 patients with chronic liver disease were enrolled and they underwent a detailed history, clinical examination, hematological and biochemical investigations, ultrasonography with portal venous Doppler, upper gastro intestinal endoscopy and hormonal evaluation. 50 age and sex matched controls were enrolled. Hypothyroidism was studied in relation to chronic liver disease and correlation of free triiodothyronine with Child-pugh score.

In practical clinical terms diagnosis of chronic liver disease is made in the presence of duration >6 months, indicative clinical features, with serum and imaging results. Therefore, the utilization ofclinical (signs and symptoms of liver cell failure), bio-chemical (raised bilrubin, SGOT, SGPT,low albumin),hematological(low hemoglobin, platelets and leucocyte count) and radiological(absence of thin hyper echoic line, paucity of peripheral hepatic vessels, accentuated

echogenic walls of the portal vein, nodular liver cirrhosis, contracted, signs of portal hypertension) tools is vital in diagnosis of chronic liver disease.

Patient characteristics:

50 patients with chronic liver disease were enrolled in this study with a mean age of 44.38±9.33 years(range 24-62 years). 78%(39 patients) were males and 22%(11 patients) were females. Similarly 50 controls were enrolled with a mean age of presentation 41.84±8.24. 72%(36 controls) were male and 28%(14 controls) were females.

Analysis:

This study revealed, firstly, that there is a significant occurrence of hypothyroidism in chronic liver disease patients. Secondly, there is a negative correlation of free triiodothyronine with Child-pugh score.

In this study, 12% patients (6 patients) with CLD have hypothyroidism. Out of which 4%(2 patients) are subclinical hypothyroidism, 2%(1 patient) is overt hypothyroidism and 6%(3 people) are secondary hypothyroidism. Various authors have reported that prevalence of thyroid hormone abnormality ranged from 13% to 61%. In patients with cirrhosis, hypothyroidism was more frequently seen, and hyperthyroidism has also been reported[59]. This is due to varied etiology and severity. In a study by Sandeep kharb et al[48] 4(5.33%) patients out of 75 patients of liver disease found to be hypothyroid, in which 3(3.5%) were subclinical and 1(1.3%) patient is overt hypothyroid. Out of 30 patients of liver cirrhosis in a study conducted by K.V.S.Harikumar et al[50] shows subclinical hypothyroidism is present in 10%(3 patients), central hypothyroidism in 6.66%(2 patients) and primary hypothyroidism in 3.3%(1patient). According to G.Deepika[49] et al in a study on 310 cirrhotic patients

revealed that cirrhotic patients weremore prevalence thyroid dysfunction specially hypothyroidismbecause of many reasons. This study also shows none of the results was statistically significant individually. But considering hypothyroidism as a single entity which includes all subtypes, it was found out to be statistically significant.

This study shows that statistically significant decrease in Mean FT3 and TSH compare to control with P value of 0.001 and 0.008 respectively. However our study shows statistically insignificant increase in FT4 level. These findings does not go with the study conducted by G.Deepika et al[49] showed that there was a significantly increased between cirrhotic patients and non-cirrhotic subjects for TSH and slightly decreased T3 and T4 where the p value is 0.039, 0.014 and 0.245 respectively. These findings are not in agreement with Mohamed Abdel-Fattah El-Feki et al[51] who found that in chronic hepatitis C concluded that decrease in the FT3 and

FT4 levels and increase in the TSH levels in patients with CHC with cirrhosis when compared to patients with CHC without cirrhosis. This is in agreement with Hussein AwadMousa[54] who found that a significant decrease level of T3 and an insignificant change in TSH and T 4levels than control groups. Takahashi et al[53] concluded that serum Free T3 (FT3) levels reduced in CLD in order of CPH, CAH and LC, and were low levels in AH with the same degree as LC.

Liver disease is also associated with increase in inflammatory cytokines that negatively affect hypothalamo thyroid axis,[71,72] which may explain lower TSHlevels (statistically not significant) observed in patients with liver disease as compared to controls. This may be the hypothesis for central hypothyroidism in our study. Ilias, I., et al., [73]found that in cases of prolonged illness, hypothalamic- pituitary suppression usually occurred. This leads to decreased secretion of TSH, decreased T4 production by the thyroid

gland. Several lines of evidence suggest a reduced dopaminergic tone as a consequence of the accumulation of false neurotransmitters, which might be responsible for raised basal TSH concentrations, as dopamine has been shown to exert an inhibitory effect in the regulation of TSH secretion[74]. Antonelli, A., et al[74]disagreed with our study who found that the level of TSH was significantly higher in patients with CHC. Increase in total T4 has been observed in patients with acute and CLD due to increase in TBG levels, which is synthesized as acute phase reactant[10]. It can be stated that in the initial state of acute liver diseases the total T4 production increases and subsequently as liver function is worsen it will reduced due the higher and low concentration of TBG, respectively.

Our study FT3 is significantly lower in case groups with a mean of 2.44 as compared to control group with a mean of 2.81with P value of <0.001.FT3 is found tobe decreased in

14(28%) patients out of 50. 1(2%) out of 50 controls found to be low FT3. P value is found to be 0.0004. Among 28 patients in child pugh B FT4 is found to be decreased in 4(14.29%) patients. Out of 22 patients in child pugh C FT3 is found to be decreased in 10(45.45%) patients. The correlation co-efficient of FT3 with CTP is found to be -0.57 with P <0.001, found that FT3 is negatively correlated with CTP.

This is in agreement withFariborz Mansour-Ghanaei et al[55] reported that a negative correlation was found between Child-Pugh scores and total serum T3 level (r = -0.453, P < 0.001). Also a reverse correlation was observed between MELD score and T3 levels (r = -0.305, P = 0.14) and concluded that concluded that serum T3 concentration is a good index of hepatic function, decreasing by the severity of liver damage. HusseinAwadMousa et al,.[54] concluded that signi□cant decrease level of T3 (p value <0.05) in cirrhotic patients than controls.This goes with M Borzio et al[8] who evaluated

thyroid function in 33 patients with liver disease and found that T3, FT3 and T3/thyroxine binding globulin and thyrotropin after thyrotropin releasing hormone were significantly reduced. According to kahashi H et al[53] conducted a study on thyroid hormones in different categories of liver disease like acute hepatitis, chronic persistent hepatitis and chronic aggressive hepatitis concluded that Serum Free T3 (FT3) levels reduced in CLD in order of CPH, CAH and LC, and were low levels in AH with the same degree as LC. This is in agreement with Sandeepkharb et al[48] who studied thyroid function in over 75 patients with AH, CLD and LT group concluded that Among patients with LT and AH groups, the only abnormality was significantly lower total T3 compared with healthy controls. This result goes with Sanu A at al[56] who found that serum T3 and FT3 showed an inverse correlation with serum bilirubin and positive correlation with serum albumin.

One more observation in our study shows TSH is found to be negatively correlated with Child-pugh score with correlation co-efficient of -0.176 but it is found to be statistically insignificant with P value of 0.2224. this is agreement with Oren R et al[52] who found a significant negative correlation was found between thyroid-stimulating hormone blood levels and both functional and synthetic liver function tests ($p < 0.001$).

In this study revealed that decreased total T3 probably reflects a decrease in deinodinase1 activity in the liver of cirrhotic patients[75,76,64]. Several studies concluded that the most consistent thyroid hormone profile in patient with cirrhosis is low total and free T3 and elevated rT3 levels, similar to changes in patients with sick euthyroid syndrome. This results in a decrease in conversion of T4 to T3. The T3:Rt3 ratio parameter of liver function[60,61,62-66].

Although some T3 is produced in the thyroid, approximately 80-85 percent is generated outside the thyroid, primarily by conversion of T4 in the liver and kidneys.[30,31]

LIMITATIONS OF THE STUDY:

- As this was a cross sectional study we could not access factors which could have predicted mortality and morbidity.
- Our study data derived from a small group of patients do not give enough evidence to suggest that the observed endocrinopathies are merely coincidental or due to the underlying cirrhosis. Further large scale studies with more number of patients are required to confirm the findings observed in our study.

CONCLUSION AND RECOMMENDATIONS

This study revealed, firstly, that there is a significant occurrence of hypothyroidism in chronic liver disease patients. Secondly, there is a negative correlation of free triiodothyronine with Child-pugh score.. The present study revealed that cirrhotic patients had more prevalent thyroid dysfunction specially hypothyroidism because of many reasons.

The liver has important role in thyroid hormone metabolism because it is themanufacturer of protein that bind thyroid hormone, such as thyroid-binding globulin (TBG), pre-albumin and albumin. It is also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation, biliary excretion, oxidative deamination and the extra thyroidal deiodination of thyroxin (T4) to triiothyronine (T3) and to reverse T3. On the other hand the level of thyroid

hormone is also important to normal hepatic function and bilirubin metabolism[77,78].

Conceivably, the disorders of these two organs would interact or influence each other. As liver abnormalities worsen the T3 production from T4 is also reduced. It is believed this reduction of T3 which mainly correspond to even lower basic metabolism rate, economically can be useful due to preventing extra energy waste and keep it for the onset of liver disease or any other related syndrome which consume further energy. Free T3 concentration corresponding with the state of liver disease and it seems the serum T3 concentration directly related to liver abnormalities progress. The low total and FT3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal BMR within hepatocytes and preserve liver function and total body protein stores. It has been suggested that low FT3 may confer a survival advantage, which adapts an organism to chronic illness by reducing the

basal metabolic rate within cells and thereby reducing caloric requirements. Oren R, Sikuler et al[68]concluded that hypothyroidism has also been associated with lesser degrees of decompensation in cirrhosis.[38] Controlled induction of hypothyroidism might therefore be beneficial in cirrhotic patients, but further studies are required to test this hypothesis. Also in stable cirrhosis, a state of hypothyroidism has been shown which correlates with slow progression of stage of cirrhosis[52,68].Few studies have reported that the low thyroid hormones are independent predictors of mortality in patients admitted to intensive care units (ICU), suggesting the inclusion of the thyroid profile in these scoring systems[79-81].

In conclusion, thyroid dysfunction forms important part of spectrum of Chronic liver disease. Deterioation of functions of liver disease predicts presence of thyroid dysfunction and these patients should be evaluated for thyroid dysfunction periodically.

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Kanyakumari Govt. Medical College
Asaripallam 62 9201

Dated: 09.09.2016

CERTIFICATE OF ETHICAL COMMITTEE APPROVAL

The Institutional Ethical Committee meeting was conducted on 9.9.2016 at 11.00 am at Medical Education Unit, Kanyakumari Govt. Medical College Asaripallam, to give approval of your study title "OCCURRENCE OF HYPOTHYROIDISM IN CHRONIC LIVER DISEASE AND CORELATION OF FREE TRIIDOTHYRONINE WITH CHILD PUGH SCORE"

The following members of the Ethical Committee attended the Meeting.

1. Chairman : Dr. M. Kannan. M.D.,
Prof of Anaesthesia (Retired)

2. Basic Medical Scientists : 1.Dr. R. Rajesh M.D.,
Assoc. Professor & HOD of Forensic Medicine
Kanyakumari Govt. Medical College Asaripallam

2. Dr. K.U. Suresh Balan M.D.,
Associ. Prof & HOD of Community Medicine
Kanyakumari Govt. Medical College Asaripallam

3. Clinicians : 1. Dr. Usha M.S.,
Prof. & HOD of Surgery
Kanyakumari Govt. Medical College Asaripallam

2. Dr. Prince Sree Kumar Pius M.D.,
Prof. of Medicine
Kanyakumari Govt. Medical College Asaripallam

3. Dr. J. Chitra M.D.,
Prof. & HOD of Obstetrics & Gynaecology
Kanyakumari Govt. Medical College Asaripallam

4. Dr. A.J.S Pravin M.D.,
Prof. & HOD of Dermatology
Kanyakumari Govt. Medical College Asaripallam

5. Dr. J.A. Jayalal M.S .,
Assoc. Prof. of Surgery,
Kanyakumari Govt. Medical College Asaripallam

6. Dr. Edward Johnson M.D.,
Assoc. Prof. of Anaesthesia,
Kanyakumari Govt. Medical College Asaripallam

4.	Representative of Non Government Voluntary Agency	:	Mrs. Jesintha Dharma
5.	Theologian	:	Dr. Surendra M.A, M.Phil, M.Ed.,Ph.D.,
6.	Statistician	:	Dr. J. Merlin Premala Ph.D
7.	Lay Person	:	Thiru. Justin OP Block (May I Help You) KGMCH Asaripallam
8.	Member Secretary	:	Dr. T. Ashok Kumar M.D., Prof & HOD of Pharmacology Kanyakumari Govt. Medical College Asaripallam

The committee has given approval of your study subject to the following conditions

- The Study should be conducted in its presented form.
- The Progress of the study and any changes in the study to be informed to the committee
- Copy of the final result of study may be furnished to the committee.

Member Secretary
Institutional Ethical Committee
Kanyakumari Govt Medical College
Asaripallam

MEMBER SECRETARY
INSTITUTIONAL ETHICAL COMMITTEE
KANYAKUMARI GOVT. MEDICAL COLLEGE
ASARIPALLAM - 629 201

Chairman
Institutional Ethical Committee
Kanyakumari Govt Medical College
Asaripallam

CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
KANYAKUMARI GOVT. MEDICAL COLLEGE
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To
Dr. Chandrashekar M
PG in MD General Medicine
Dept. of General Medicine
KGMC Asariapallam

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Urkund Analysis Result

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Submitted By: doctorchandujune17@gmail.com
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Sources included in the report:

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ezhil intro.doc (D31018840)
2011-07-12_0201156.pdf (D4265265)
http://www.thyroidmanager.org/chapter/thyrotoxicosis-of-other-etiologies/
http://dx.doi.org/10.1093/qjmed/hch088

Instances where selected sources appear:

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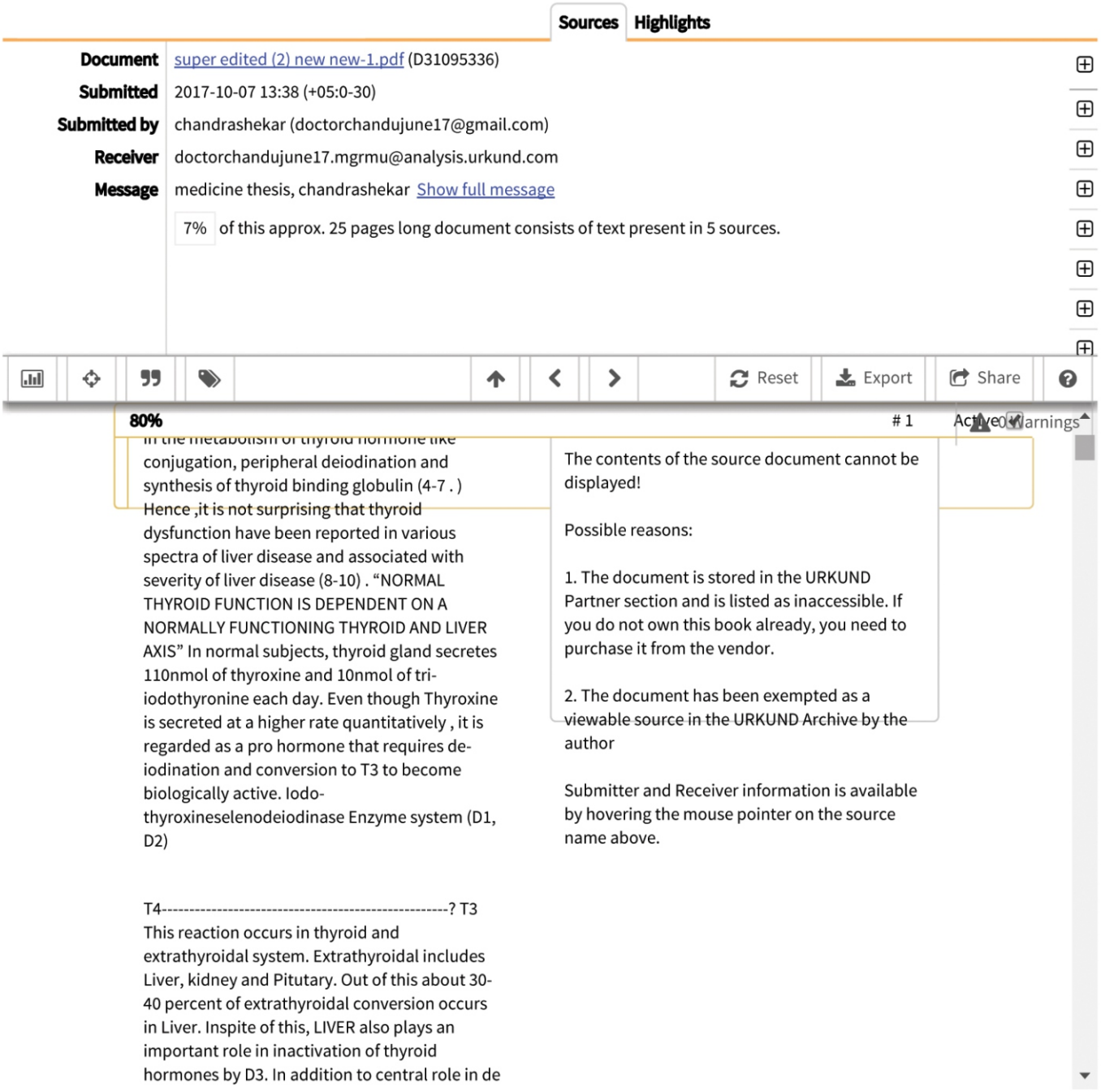
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conjugation, peripheral deiodination and synthesis of thyroid binding globulin (4-7 .) Hence ,it is not surprising that thyroid dysfunction have been reported in various spectra of liver disease and associated with severity of liver disease (8-10) . “NORMAL THYROID FUNCTION IS DEPENDENT ON A NORMALLY FUNCTIONING THYROID AND LIVER AXIS” In normal subjects, thyroid gland secretes 110nmol of thyroxine and 10nmol of tri-iodothyronine each day. Even though Thyroxine is secreted at a higher rate quantitatively , it is regarded as a pro hormone that requires de-iodination and conversion to T3 to become biologically active. Iodo-thyroxineselenodeiodinase Enzyme system (D1, D2)
T4----------? T3
This reaction occurs in thyroid and extrathyroidal system. Extrathyroidal includes Liver, kidney and Pituitary. Out of this about 30-40 percent of extrathyroidal conversion occurs in Liver. Inspite of this, LIVER also plays an important role in inactivation of thyroid hormones by D3. In addition to central role in de
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